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Journal Pre-proof

"Incidence and predictors of development of new onset hypertension post COVID-19 disease"

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Title Page

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Title: "Incidence and predictors of development of new onset hypertension post COVID-19 disease"

Running title: "Does hypertension cause post COVID-19 disease?"

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Keywords:

Baroreflex, Endothelial injury, Hypertension, Inflammation, Post covid outcome

Conflict Of Interest

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Incidence and predictors of development of new onset hypertension post COVID-19 disease

Abstract:

Aims

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) affects vital organs and causes vascular injury. There are concerns that this injury may have long-term consequences on the cardiovascular system after recovery from COVID-19. We investigated the incidence and predictors of new-onset hypertension at 1-year follow-up post-COVID-19 disease.

Methods:

In this prospective observational study, 393 patients hospitalised and diagnosed with COVID-19 disease at a tertiary cardiac care hospital during 27th March 2021 to 27th May 2021. Eligible 248 patients whose baseline characteristics, laboratory findings, treatment and outcome data were received systematically. Patients were followed up at 1 year of COVID-19 disease recovery.

Results:

We found that 32.3% of the population had new onset of hypertension at 1 year follow-up post-COVID-19 disease recovery. More hypertensive patients had severe computed tomography (CT) score severity (28.7 vs 14.9%; P 0.02). More number of patients in the hypertensive group were treated with steroids (73.8% vs 39%; p<0.0001) during hospital stay. In-hospital complications were higher (12.5 vs 4.2%; P 0.03) in the hypertensive group. Patients who developed new-onset hypertension had statistically significantly higher baseline values of serum ferritin and C-reactive protein (CRP) (P 0.02 and 0.03 respectively). Vascular age was found 12.5± 3.96 years more than chronological age in hypertensive patients.

Conclusion:

New onset of hypertension was detected in 32.3% of patients at one-year follow-up post-COVID-19 disease recovery. Severe inflammation at the time of admission and severe CT severity score were associated with the development of new onset of hypertension on follow-up.

Keywords:

Baroreflex, Endothelial injury, Hypertension, Inflammation, Post covid outcome

Key message:

In acute phase SARS-CoV-2 infection causes vascular damage via various mechanisms. Vascular complications occurring at different points in the course of the disease are worrisome as that can cause vital organ damage. At one-year follow-up post-COVID-19 disease recovery, new onset of hypertension was detected in 32.3% of patients in Indian population.

Introduction

On March 11, 2020, the new coronavirus (COVID-19) burst was declared as a global pandemic by the World Health Organization.[1] This epidemic poses a massive threat to human health worldwide. Globally, 17.95% COVID-19 incidence was sustained by India. SRRS-COV-2 virus infection can affect multiple organ systems. SRRS-COV-2 virus infection can affect multiple organ systems. [2] It can cause a wide range of symptoms ranging from mild to severe including fever, cough, shortness of breath and loss of smell and taste. SARS –COV-2 infection causes dysregulation of immune, thrombotic and renin-angiotensin-aldosterone (RAA) balance which results in vascular endothelial injury and dysfunction. [3] COVID-19 disease is also considered as a vascular disease. The vascular damage caused by SARS-COV-2 infection may have long-term consequences post-COVID-19 recovery including hypertension, acute coronary syndrome and stroke. Long term effects of COVID-19 disease are not completely known. The post-covid-19 disease identifies potential long-term adverse outcomes and new-onset comorbidities. [4] A large number of studies have pointed to the high prevalence of hypertension and the significantly higher mortality rate among hypertensive patients hospitalised with COVID-19.[5-7] While COVID-19 is primarily a respiratory disease, emerging evidence suggests that it can also cause cardiovascular complications including hypertension.[8] The impact of COVID-19 disease on blood pressure (BP) has not yet been firmly demonstrated. The present study investigated the incidence and predictors of new-onset hypertension at 1-year follow-up post-COVID-19 disease.

Materials and methods:

Study design:

This retro prospective observational study included clinical data of 393 patients admitted and diagnosed with COVID-19 disease at a tertiary cardiac care hospital between 27th March 2021 to 27th May 2021. After applying inclusion and exclusion criteria, 248 eligible patients were identified and data of these patients was analyzed.

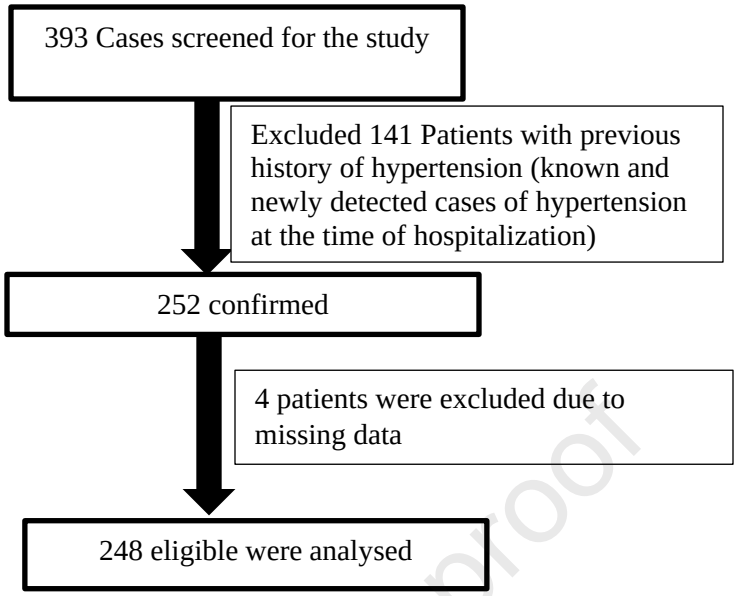
Inclusion Criteria

- Age between 30 to 74 years
- The patients diagnosed as COVID-19 Positive by RT PCR tests, radiology and laboratory findings and admitted to the institute according to the guideline of the Government of India Ministry of Health and Family Welfare were included in this study. [9]
- COVID-19 admitted recovered patients who came at one year follow up

Exclusion Criteria

- Patients with a previous history of hypertension, kidney or liver failure, major illness
- Missing information from individuals who left the follow-up

We scheduled 12 month follow-up of patients post hospital discharge for COVID-19 disease at our tertiary cardiac care hospital. At the time of follow up; out of 393 patients,14 patients were detected having hypertension at the time of hospital admission and 127 patients had prior history of hypertension and they were already on antihypertensive medications before acquiring COVID-19 disease. These 141 patients were excluded from the study due to previous history of hypertension and 4 patients due to missing data were not included in the study. Finally, 248 eligible patients were analyzed.



Flow chart

The patient's baseline characteristics, laboratory findings, treatment and outcome data were received systematically from electronic medical record system. All vital parameters such as pulse, blood pressure, temperature, respiratory rate, and peripheral capillary oxygen saturation (SpO2) were recorded by the medical officer at the time of 1 year follow up. General and systemic examinations were performed and recorded in the case sheet. At the follow-up, blood was drawn to test the complete blood count, C-reactive protein, D-Dimer, HbA1c, and lipid profile using International Federation of Clinical Chemistry (IFCC) approved enzymatic methods on an auto-analyzer using a commercially available kit (ARCHITECH PLUS ci4100, Germany). Lipid levels were classified using guidelines from the National Cholesterol Education Program (NCEP) and Adult Treatment Panel III (ATP III).[10] All co-morbidities like diabetes mellitus-II, dyslipidemia, chronic kidney disease (CKD), etc. were also recorded.

Using the Framingham Vascular Age Calculator, the vascular age of every patient was determined. Vascular age estimations were carried out in accordance of D'Agostino et al CVD risk prediction using lipids. (https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-

year-risk/).[11] According to the Framingham Vascular Age Calculators, we had included only people who were between the ages of 30 to 74. Age, gender, smoking, total cholesterol level, systolic blood pressure, and diabetes were all evaluated as risk variables.

The term "new onset of hypertension" was coined as greater or equal to 140 mmHg systolic BP and/or 90 mmHg diastolic BP according to the European Society of Cardiology Guidelines (2021).[12] According to this guideline we divided our patients into two groups: Hypertension (≥140 mmHg systolic BP and/or ≥90) and normotensive (<140 mmHg systolic BP and/or <90). Blood pressure was measured under resting conditions. Blood pressure was measured on the right upper arm in the seated position by the medical officer using a sphygmomanometer. We took 3 readings at a 1-minute interval. We used the average of the last 2 readings for final consideration. The institutional ethics committee approved the study. (UNMICRC/Allied/2021/18)

Statistical Analysis:

Using SPSS 26.0 software (IBM, Inc., Chicago, IL, USA), the categorical variables are expressed as frequencies (percentages), and the continuous variables are expressed as the mean ± standard deviation. The Chi-square test was used for categorical variables. Pearson correlation was used to find out the correlation between the variables. In a multivariate analysis, a logistic regression model was used. A P-value < 0.05 was considered statistically significant.

Results:

Out of 393 patients, eligible 248 COVID-19 patients with 169(68.1%) males and 79(31.9%) females were enrolled. Table 1 shows the demographic and baseline characteristics of the patients. Our study showed out of 248 patients new onset of hypertension in 80(32.3%) patients at 1 year follow-up post-COVID-19 disease. The mean age of all patients was 51.16± 12.71 years. We divided 248

patients in hypertensive (N=80) and normotensive (N=168) groups. Radiologically, more hypertensive patients had severe CT score severity (28.7 vs 14.9%; P 0.02) than normotensive patients. The present study shows the prevalence of hypertension was high in the male (75%) gender without statistical significance. During COVID-19 illness, patients were managed in the hospital according to severity. More number of patients in the hypertensive group were treated with steroids (73.8% vs 39%; p<0.0001) during hospital stay.

In-hospital complications were found in 17 patients. Out of 17 patients, 9 had a myocardial infarction, two patients had deep vein thrombosis, one patient had pulmonary thromboembolism, one patient had heart failure (LVEF=20 and known case of old AWMI), one had a cerebrovascular stroke, two had ventricular tachycardia and one had acute limb ischemia. In-hospital complications were higher (12.5 vs 4.2%; P 0.03) in the hypertensive group than in the normotensive group.

Baseline laboratory findings at the time of admission are shown in table 2. Most of the laboratory findings were high in hypertensive patients; but the difference was only statistically significant in C-reactive protein(CRP-Q) (74.32±69.27 vs 54.04±57.51 mg/L; P 0.02), serum ferritin levels (631.94±546.69 vs 481.42±497.37 ng/mL; P 0.03) and platelet count (262833.33±228817.59 vs 209146.95±90108.17 mcL; P 0.01) at the time of admission. Higher baseline CRP-Q (>5UNL, >50 mg/L) levels were found in the hypertensive group than in the normotensive group (51.2 vs 33.3%; P 0.007). Higher baseline D-dimer levels characterized by >500 ng/L were found more in the hypertensive group than the normotensive group (73.8 vs 60.1%; P 0.03). Higher baseline trop-I levels (>3 UNL) were found in the hypertensive group as compared to the normotensive group (16.3 vs 7.7%; P 0.04)

We also calculated the vascular age and 10 years of CVD risk score of all the patients and compared them with the chronological age of the patients. The mean difference between vascular and

chronological age in hypertensive patients was significantly higher (12.50±3.96 years) than in normotensive patients (5.48± 4.73 years); the mean difference of 10 years' risk of cardiovascular disease was (4.91±0.01%) and the statistically significant (P <0.0001).

Table 3 shows follow up laboratory findings and vascular age calculation at 1 year follow up. Differences in laboratory results were not statistically significant.

A logistic regression model is given in the table.4 showed severe CTSS 1.26(95% CI 1.08-1.46; P 0.04), baseline CRP levels at the time of admission 1.28(95% CI 1.02-1.42; P 0.02) and treatment with steroid 1.83(95% CI 1.19-2.21; P 0.01) as independent predictors of new-onset hypertension in COVID-19 recovered patients.

Discussion:

This post-COVID-19 observational study designed to assess incidence and predictors of newly detected hypertension in COVID-19 patients in the Indian cohort (N=248). Moreover, present work gives some of the most significant findings concerning hypertension in COVID-19 recovered patients. At the time of follow-up, we noticed that patients who did not have a past history of hypertension also had increased systolic and diastolic blood pressure. Surprisingly we found that out of 248 patients 80 (32.3%) patients had new onset of hypertension at 1-year follow-up post-COVID-19 disease recovery.

We observed in our study that COVID-19 occurred in a majority of the middle or older age group. Shikha Jain et al reported a similar finding. [13] Present study showed the dominance of males in COVID-19 cases. This is comparable to other studies showing a high proportion of cases among males. (14,15). Some studies have suggested the role of active immune response in women triggered by mast cells may help them in fighting infectious diseases better than males. [14,15]

Studies conducted in different parts of the world have shown that the presence of comorbidities increases the severity of COVID-19 disease. [16] The meta-analyses which included 18 studies (N=14,558) reported the prevalence of hypertension in 22.9%, diabetes mellitus-II in 11.5% and chronic kidney disease in 2.4% of patients with COVID-19 disease. [17-20] Despite having a large number of COVID-19 patients, only a few large studies on the prevalence of comorbidities in COVID-19 patients from India are currently available.[21-22] Almazeedi S et al single centre study reported 14% comorbidities in Indian population like hypertension, diabetes, COPD/Asthma, CAD and CKD. (22) In contrast, the present study shows 27.8% comorbidities which were higher than other studies. Predictably, Indian COVID-19 patients had the highest prevalence rate of diabetes compared to patients from other countries.[22,23]

CT severity score has a vital role in the detection of the severity of lung involvement and predicting the outcome of COVID-19 patients. CT score had a strong correlation with the worse outcome with comorbidities. The present study showed that severe CT score was found in 28.7% of hypertensive patients as compared to 14.9% of normotensive patients (P 0.02). Apart from CTSS, various other inflammatory markers have been discovered to be independent predictors of severe disease and outcome in COVID-19 patients. A study done by Luca et Zanoli et al reported that higher CRP levels at the time of admission were associated with higher aortic stiffness at 12 to 48 weeks post-recovery.[24] We found in our study that those patients who developed new-onset hypertension had statistically significant higher baseline values of s.ferritin and CRP (P 0.02 and 0.03 respectively). Also, higher baseline values of D-Dimer (>500 ng/L), CRP (>50 mg/L) and Trop-I (>3unl) were found in our study in the hypertensive group as compared to a normotensive group with statistical significance. As newly detected hypertensive patients had higher severe CTSS and higher

inflammatory and other prognostic laboratory markers at baseline, it suggests that these patients had the more severe disease at baseline.

Most of the long-term COVID-19 follow-up studies showed that COVID-19 disease is associated with post-discharge consequences.[25] Long-term post-COVID-19 sequelae studies will improve understanding of the natural history of COVID-19 disease and the factors or mediators involved.[26] One of the study conducted by Daniel Ayobukhani et al; on the largest cohort (N=47780) reported that patients discharged from the hospital post COVID-19 infection had higher rates of diabetes mellitus-II (P <0.0001) and cardiovascular disease (P <0.0001).[26] In the present study, elevated levels of HbA1c and lipid profile were found on follow up but the difference was not statistically significant (P 0.19). Guiling Li et al reported that Both LDL-c, HDL-c and TC were significantly higher at follow-up. [27] While in our study, we found a deranged lipid profile in the hypertensive group but the difference was insignificant statistically.

Viral infections can alter epigenetic age. Acceleration of epigenetic aging caused by COVID-19 may produce COVID -19 syndrome post recovery from acute infection. [28] Our findings showed that the vascular age of hypertensive patients was significantly higher than chronological age on follow-up. Vascular age was found 12.5± 3.96 years more than chronological age in hypertensive patients. Though the presence of hypertension is one of the parameters for the calculation of vascular age, there are other parameters like a history of smoking, age, gender, total Cholesterol levels and diabetes, and treatment of hypertension which are taken into account for the calculation of vascular age. This suggests that COVID-19 disease may cause premature vascular aging and increase future cardiovascular risk.

There are various mechanisms by which the SARS-COV-2 virus causes vascular injury in the acute phase. SARS-COV-2 causes dysregulation of the inflammatory response, immune response, and

thrombotic and renin-angiotensin-aldosterone system response. SARS-CoV-2 enters the target cell using the angiotensin-converting enzyme 2 (ACE2). ACE2 is a key component in the RAA system for the regulation of blood pressure. The SARS-CoV-2 infection leads to activation of the RAA system which results in endothelial injury and dysfunction.[3] Mild chronic inflammation post-acute phase recovery may alter elastic properties of the arterial wall due to reduced smooth muscle cell relaxation and changes in the arterial wall structure as a consequence of endothelial injury.[24] Infection with SARS-CoV-2 can cause baroreflex dysfunction.[29] Baroreflex dysfunction is linked with arterial stiffening.[30] Though the exact mechanism of the development of hypertension post-COVID-19 disease is unknown, dysfunction of RAAS. Baroreflex dysfunction and arterial stiffness may be contributory. As COVID-19 disease has already affected a large population by now, an understanding of underlying mechanisms and the long-term impact of COVID-19 on blood pressure is needed.

Limitations of the study:

The current study was conducted in a single center and included a small number of patients. The follow-up time frame was short. long-term follow-up studies should be planned to conduct more research to determine how COVID-19 disease causes hypertension. Due to the lack of lipid profile data of the cohort at the time of admission, the baseline vascular age of the cohort is not known.

Conclusion:

At one year of follow-up post-SARS-COV-2 infection, almost one-third (32.3%) of patients developed new-onset hypertension. More severe disease characterized by higher CTSS, higher baseline CRP levels and treatment with steroids for the control of disease were found to be associated with the development of hypertension on follow-up. Patients who recovered from the severe

COVID-19 disease and were treated with steroids should be screened for hypertension on follow-up.

Notes

Conflict Of Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval:

The study has been approved by the institutional ethics committee (UNMICRC/Allied/2021/18, 16 September 2021).

Informed Consent:

Informed consent was obtained from all individual participants

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Table legends:

Table:1 Demographic and baseline characteristics

Table:2 Baseline laboratory findings at the time of admission

Table:3 Follow up laboratory findings and vascular age calculation at 1 year follow up

Table:4 Logistic regression analysis

Table:1 Demographic and baseline characteristics

Variables	**Hypertensive** **N=80(32.2%)**	**Normotensive** **N=168(67.7%)**	**P-value**
Age	52.39±12.64	50.35±13.91	0.23
Gender			
Male	60(75%)	109(64.9%)	0.15
Female	20(25%)	59(35.1%)	
BMI	26.3±4.03	26.56±4.79	0.68
Diabetes mellitus-II	25(31.3%)	51(30.4%)	1.0
Smoking	1(1.3%)	2(1.2%)	0.56
Chronic kidney disease	1(1.3%)	2(1.2%)	0.56
K/C/O CAD	5(6.3%)	4(2.38%)	0.14
Severe CT severity score	23(28.7%)	25(14.9%)	**0.02***
In-hospital complication	10(12.5%)	7(4.2%)	**0.03***
Treatment			
Remdesivir	58(72.5%)	118(70.2%)	0.83
Steroids	59(73.8%)	66(39%)	**<0.0001***
Other immunosuppressant's	4(5%)	4(2.4%)	0.48

BMI- Body mass index, CAD-Coronary artery disease; CT-Computed tomography, *P value <0.05 statistically significant

Table:2 Baseline laboratory findings at the time of admission

	Hypertensive N=80(32.2%)	**Normotensive N=168(67.7%)**	**P-value**
Haemoglobin (g/dl)	11.85±1.61	12.05±1.84	0.41
Total Count (cmm)	7128.08±4672.65	6779.03±4458.91	0.57
Platelet Count (mcL)	262833.33±228817.59	209146.95±90108.17	**0.01***
D-Dimer (ng/L)	1814.03±2316.84	1587.89±2364.06	0.49
Troponin-I (ng/L)	1245.7±6470.93	601.44±4628.03	0.41
BNP (ng/L)	116.25±107.92	133.84±286.49	0.60
CRP-Q (mg/L)	74.32±69.27	54.04±57.51	**0.02***
S. Ferritin (ng/mL)	631.94±546.69	481.42±497.37	**0.03***
HBA1C (%)	6.72±2.24	6.58±2.01	0.65
RBS (mg%)	176.48±103.61	171.20±103.8	0.74
SGPT (U/L)	56.95±57.74	59.96±114.05	0.83
S.creatinine (mg/dl)	1.08±0.27	1.04±0.28	0.29

BNP- Brain natriuretic peptide, CRP-Q- C-reactive protein, HbA1c- Glycosylated hemoglobin, RBS- Random Blood Sugar, SGPT- Serum glutamic pyruvic transaminase, *P value <0.05 statistically significant

Table:3 Follow up laboratory findings and vascular age calculation at 1 year follow up

Variables	**Hypertensive N=80(32.2%)**	**Normotensive N=168(67.7%)**	**P-value**
D-dimer (ng/L)	363.14 ± 250.05	342.33 ± 484.79	0.72
HBA1C (%)	6.04 ± 1.48	5.81 ± 1.2	0.19
Haemoglobin (g/dl)	13.95 ± 1.49	13.69 ± 1.75	0.35
Cholesterol (mg/dl)	180.19 ± 39.11	175.61 ± 39.77	0.50
LDL/HDL Ratio	2.83 ± 0.97	2.74 ± 1.1	0.41
LDL (mg/dl)	109.35 ± 32.58	105.38 ± 35.89	0.46
S.HDL Cholesterol (mg/dl)	39.47 ± 9.22	40.4 ± 9.55	0.59
Total Chol / HDL Ratio	4.65 ± 1.3	4.51 ± 1.24	0.52
Total Lipids (mg/dl)	676.74 ± 100.47	665.13 ± 117.27	0.32
Triglyceride (mg/dl)	157.08 ± 78.03	149.12 ± 99.95	0.20
VLDL (mg/dl)	31.37 ± 15.61	29.84 ± 19.99	0.21
Platelet count (cmm)	12280.01 ± 60970.23	17449.99 ± 65490.99	0.16
WBC (cmm)	7.76 ± 1.69	7.91 ± 2.19	0.99
Vascular age (years)	65.59 ±15.83	55.72 ±17.76	**<0.0001***
10 years risk of CVD (%)	15.40 ±9.32	10.49 ±9.33	**<0.0001***

HbA1c- Glycosylated hemoglobin, LDL- low-density lipoprotein, HDL-High density lipoprotein, VLDL-Very low-density lipoprotein, CVD- Cardiovascular disease, *P value <0.05 statistically significant

Table:4 Logistic regression analysis

Variables	**Exp (B)**	**95% C.I. for Exp (B)**		**P-value**
		Lower	**Upper**	
CTSS	1.26	1.08	1.46	**0.04***
In-hospital complications	0.22	0.04	1.18	0.08
Steroids	1.83	1.19	2.21	**0.01***
CRP-Q (mg/L)	1.28	1.02	1.42	**0.02***
S.Ferritin (ng/mL)	1.0	1.00	1.09	0.08

CTSS-Computed tomography severity score, CRP-Q- C-reactive protein, *P value <0.05 statistically significant